PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
2003946-0022(VD1207)		

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 02/40744	18.12.2002	28.12.2001

International Patent Classification (IPC) or both national classification and IPC
C07D309/10

Applicant
EISAI CO. LTD. et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.07.2003	19.02.2004

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 02/40744

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Claims, Numbers

1, 22-26, 43 received on 10.10.2003 with letter of 10.10.2003

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☒ the claims, Nos.: 44
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 43-64

because:

☒ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-64
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-64
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-42
	No:	Claims	43-64

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 43 to 64 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Amendments

The recitation of the variable R7 in the proviso (i.e. " R_7 is hydrogen") is considered to be allowable as being considered as an obvious omission. The proviso introduced to specifically exclude the synthetic intermediates disclosed in D4 is also allowed as well as the correction to the structure given in claims 23 to 26 (namely the replacement of "OR5" with "R5".

Novelty

The present application relates to the development of synthetic methodologies enabling access to luminacin analogs having a broad range of biological and pharmacological activities.

The family of capillary tube formation inhibitors, designated luminacins, is now completely excluded at the end of both independent claims 1 and 22.

Novelty can be therefore recognized.

inventive step

The field of angiogenesis inhibitors, as also summarized by the applicant in the description, has vast applications in the provision of medicaments for the treatment of many diseases such as cancer. In view of the need for the development of further therapeutic agents useful for treating disorders that involve angiogenic activity, the problem underlying the present application can be seen in the provision of further luminacin analogs via synthetic methodologies.

Independent claims 1 and 22 refer to the compound claim and to the pharmaceutical composition containing them respectively and represent the solution to the problem

stated above.

D1 and D2 only refer ti the natural compounds, isolated from the fermentation broth of an actinomycete starin, whereas D3 and-in particular- D4 both describe synthetic methods.
D3 on page 2069, right-hand column expressly teaches the fact that "src kinase activity is significantly up regulated in human cancers, particularly colon and breast cancers indicating the widespread role of src in human diseases".
D4 refers to the first total synthesis and establishment of absolute structure of luminacins C_1 and C_2 (which are the only luminacin compounds synthesised).

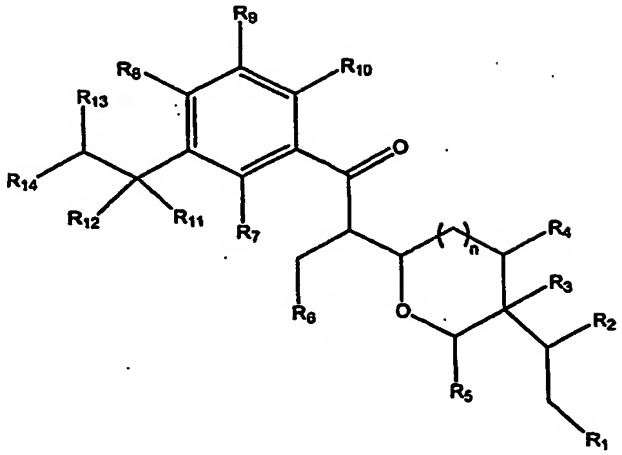
Therefore, the skilled man in the art faced with the problem of providing further derivatives/analogs via synthetic synthesis, knowing the teaching of D4, would only have taken an incentive to arrive at structurally similar natural products due to the very little synthetic variation suggested.

The compounds presently claimed are indeed structurally diverse lumicacin analogs so that an inventive step can be recognized.

Industrial applicability
For the assessment of the present claims 43 to 64 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims

1. A compound having the structure:



or pharmaceutically acceptable derivative thereof;

wherein n is 0, 1 or 2;

R_1 is hydrogen or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R_2 and R_3 are each independently hydrogen, or, when taken together, may be –O- or –$(CH_2)_q$- , wherein q is 1, 2 or 3;

R_4 is hydrogen, hydroxyl, protected hydroxyl or OR^i, or an aliphatic or heteroaliphatic moiety,

wherein R^i is an aliphatic or heteroaliphatic moiety;

R_5 is hydrogen, hydroxyl, protected hydroxyl or OR^{ii}, or an aliphatic or heteroaliphatic moiety,

wherein R^{ii} is an aliphatic or heteroaliphatic moiety, or wherein R_1 and R_5, when taken together, may form a cycloaliphatic or heterocycloaliphatic moiety comprising 6 to 12 atoms;

R_6 is hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R_7 is hydrogen, hydroxyl, protected hydroxyl, OR^{iii}, or an aliphatic or heteroaliphatic moiety,

wherein R^{iii} is an aliphatic or heteroaliphatic moiety;

R_8 is hydrogen, hydroxyl, protected hydroxyl or OR^{iv},

wherein R^{iv} is an aliphatic or heteroaliphatic moiety;

R_9 is hydrogen, $-CF_3$, -CHO, imine, hydrazone, oxime, carboxylic acid, carboxylic ester, acyl halide, ketone, amide, acetal, anhydride, dihalide, epoxide, nitrile or an aliphatic or heteroaliphatic moiety;

R_{10} is hydroxyl or protected hydroxyl;

R_{11} and R_{12} are each independently hydrogen, hydroxyl or OR^v, or an aliphatic or heteroaliphatic moiety, or, when taken together, may be –(C=O)-;

wherein R^v is an aliphatic or heteroaliphatic moiety;

and R_{13} and R_{14} are each independently hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, linear or branched, and whereby each of the foregoing aryl and heteroaryl moieties may be substituted or unsubstituted;

with the proviso that:

(a) when R_4, R_5, R_8 and R_{10} are each hydroxyl, R_7 is hydrogen, R_{13} and R_{14} are each methyl, R_2 and R_3, taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:

(i) R_1 is methyl, R_9 is hydrogen, (R_{11}, R_{12}) is (=O) and R_6 is ethyl or isopropyl;

(ii) R_1 is methyl, R_9 is CHO, (R_{11}, R_{12}) is (OMe, H) and R_6 is ethyl, propyl or isopropyl;

(iii) R_1 is methyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl, propyl or isopropyl;

(iv) R_1 is methyl, R_9 is $COCH_3$, R_{11} and R_{12} are hydrogen and R_6 is ethyl; and

(v) R_1 is ethyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl; and

(b) when R_1 is methyl, R_2 and R_3, taken together, form an epoxide, R_6 is ethyl, R_7 is hydrogen, (R_{11}, R_{12}) is (OMe, H), R_{13} and R_{14} are each methyl and n is 1, the following groups do not occur simultaneously as defined: R_4 and R_5 is OH or OBn, R_8 and R_{10} is OH or $-OCH_2OCH_3$ and R_9 is –CHO, $-CH_2OH$ or $-CH_2OTBS$.

2. The compound of claim 1 wherein n is 1 and the compound has the structure:

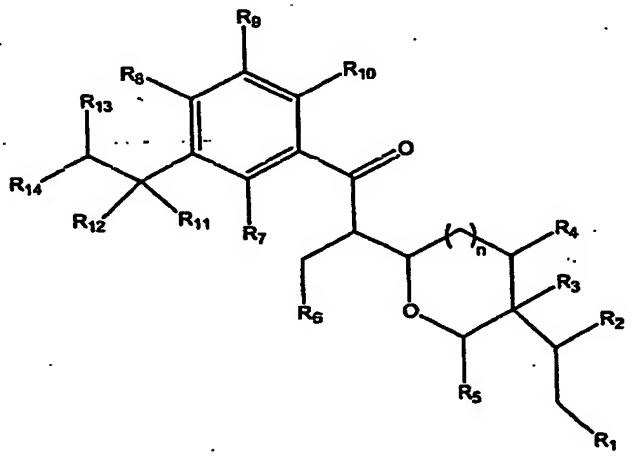
substituted or unsubstituted, branched or unbranched or cyclic or acyclic, and wherein the aryl substitutent may be substituted or unsubstituted.

20. The compound of claim 4 or 7 wherein R_{13} is lower alkyl, and wherein the alkyl substitutent may be substituted or unsubstituted, linear or branched or cyclic or acyclic.

21. The compound of claim 7 wherein R_1 is hydrogen or lower alkyl, R_5 is hydroxyl or lower alkoxyl, R_6 is lower alkyl, R_7 is hydrogen, hydroxyl, lower alkyl or lower alkoxyl, R_8 is hydrogen, hydroxyl or protected hydroxyl, R_9 is –CHO or $-CH_2OR^{vi}$, R_{11} and R_{12} are independently hydrogen or lower alkoxyl, and R_{13} is lower alkyl; wherein R^{vi} is hydrogen, protecting group or an aliphatic or heteroaliphatic moiety;

whereby each of the foregoing alkyl, alkoxyl, aliphatic and heteroaliphatic moieties may be independently substituted or unsubstituted, linear or branched, or cyclic or acyclic.

22. A pharmaceutical composition comprising:
a compound having the structure:



or pharmaceutically acceptable derivative thereof; and
a pharmaceutically acceptable carrier;
wherein n is 0, 1 or 2;
R_1 is hydrogen or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R_2 and R_3 are each independently hydrogen, or, when taken together, may be –O- or –$(CH_2)_q$- , where q is 1, 2 or 3;

R_4 is hydrogen, hydroxyl, protected hydroxyl or OR^i, or an aliphatic or heteroaliphatic moiety,

wherein R^i is an aliphatic or heteroaliphatic moiety;

R_5 is hydrogen, hydroxyl, protected hydroxyl or OR^{ii}, or an aliphatic or heteroaliphatic moiety,

wherein R^{ii} is an aliphatic or heteroaliphatic moiety, or wherein R_1 and R_5, when taken together, may form a cycloaliphatic or heterocycloaliphatic moiety comprising 6 to 12 atoms;

R_6 is hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R_7 is hydrogen, hydroxyl, protected hydroxyl, OR^{iii}, or an aliphatic or heteroaliphatic moiety,

wherein R^{iii} is an aliphatic or heteroaliphatic moiety;

R_8 is hydrogen, hydroxyl, protected hydroxyl or OR^{iv},

wherein R^{iv} is an aliphatic or heteroaliphatic moiety;

R_9 is hydrogen, $-CF_3$, -CHO, imine, hydrazone, oxime, carboxylic acid, carboxylic ester, acyl halide, ketone, amide, acetal, anhydride, dihalide, epoxide, nitrile or an aliphatic or heteroaliphatic moiety;

R_{10} is hydroxyl or protected hydroxyl;

R_{11} and R_{12} are each independently hydrogen, hydroxyl or OR^v, or an aliphatic or heteroaliphatic moiety, or, when taken together, may be –(C=O)-;

wherein R^v is an aliphatic or heteroaliphatic moiety;

and R_{13} and R_{14} are each independently hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety; and

pharmaceutically acceptable derivatives thereof;

whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, linear or branched, and whereby each of the foregoing aryl and heteroaryl moieties may be substituted or unsubstituted;

with the proviso that when R_4, R_5, R_8 and R_{10} are each hydroxyl, R_7 is hydrogen, R_{13} and R_{14} are each methyl, R_2 and R_3, taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:

(i) R_1 is methyl, R_9 is hydrogen, (R_{11}, R_{12}) is (=O) and R_6 is ethyl or isopropyl;

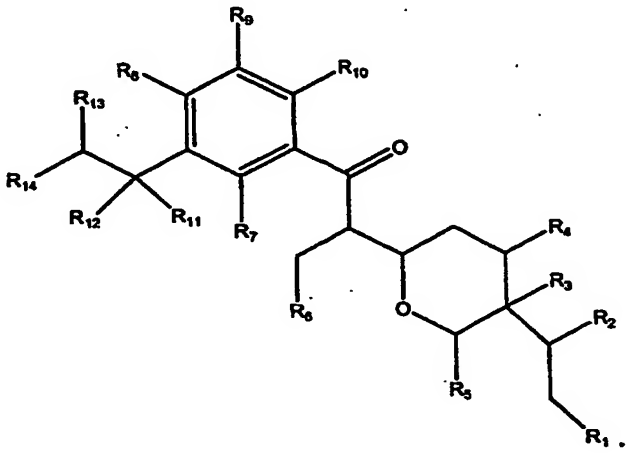
(ii) R_1 is methyl, R_9 is CHO, (R_{11}, R_{12}) is (OMe, H) and R_6 is ethyl, propyl or isopropyl;

(iii) R_1 is methyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl, propyl or isopropyl;

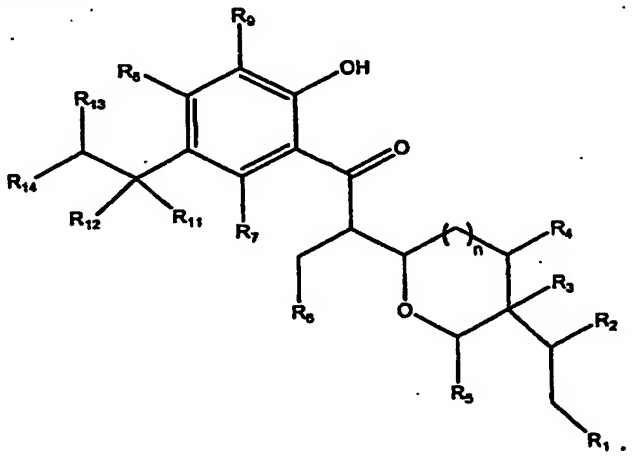
(iv) R_1 is methyl, R_9 is $COCH_3$, R_{11} and R_{12} are hydrogen and R_6 is ethyl; and

(v) R_1 is ethyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl.

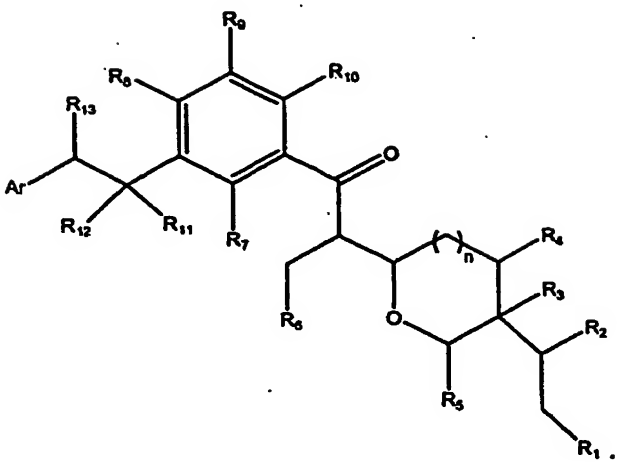
23. The pharmaceutical composition of claim 22 wherein n is 1 and the compound has the structure:



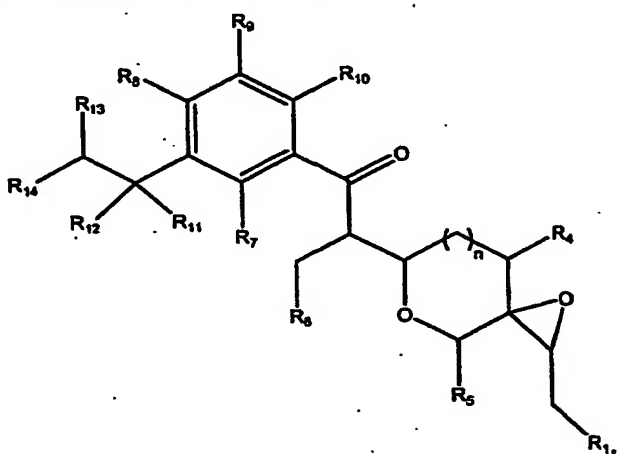
24. The pharmaceutical composition of claim 22 wherein R_{10} is hydroxyl and the compound has the structure:



25. The pharmaceutical composition of claim 22 wherein R_{14} is aryl and the compound has the structure:



26. The pharmaceutical composition of claim 22 wherein R_2 and R_3, taken together, form an epoxide, and the compound has the structure:



27. The pharmaceutical composition of claim 22 wherein R_4 is hydroxyl and the compound has the structure:

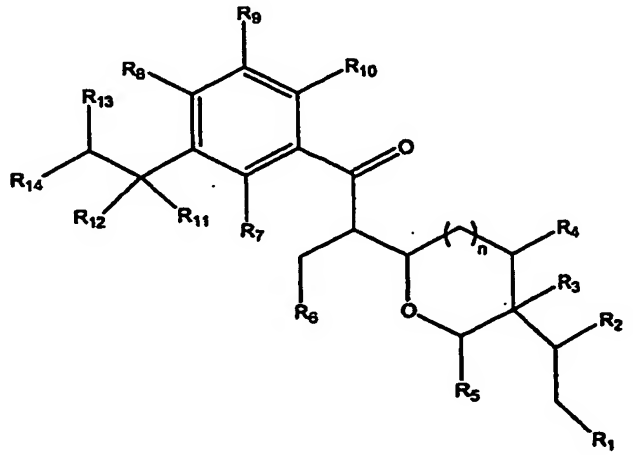
40. The pharmaceutical composition of any one of claims 22, 23, 24, 26 or 27 wherein R_{13} and R_{14} are independently hydrogen, lower alkyl or aryl, wherein the alkyl substitutent may be substituted or unsubstituted, branched or unbranched or cyclic or acyclic, and wherein the aryl substitutent may be substituted or unsubstituted.

41. The pharmaceutical composition of claim 25 or 28 wherein R_{13} is lower alkyl, and wherein the alkyl substitutent may be substituted or unsubstituted, linear or branched or cyclic or acyclic.

42. The pharmaceutical composition of claim 28 wherein R_1 is hydrogen or lower alkyl, R_5 is hydroxyl or lower alkoxyl, R_6 is lower alkyl, R_7 is hydrogen, hydroxyl, lower alkyl or lower alkoxyl, R_8 is hydrogen, hydroxyl or protected hydroxyl, R_9 is –CHO or $-CH_2OR^{vi}$, R_{11} and R_{12} are independently hydrogen or lower alkoxyl, and R_{13} is lower alkyl; wherein R^{vi} is hydrogen, protecting group or an aliphatic or heteroaliphatic moiety;

whereby each of the foregoing alkyl, alkoxyl, aliphatic and heteroaliphatic moieties may be independently substituted or unsubstituted, linear or branched, or cyclic or acyclic.

43. A method for treating cancer comprising:
administering to a subject in need thereof a therapeutically effective amount of a compound having the structure:



or pharmaceutically acceptable derivative thereof;

wherein n is 0, 1 or 2;

R_1 is hydrogen or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R_2 and R_3 are each independently hydrogen, or, when taken together, may be –O- or $-(CH_2)_q-$, where q is 1, 2 or 3;

R_4 is hydrogen, hydroxyl, protected hydroxyl or OR^i, or an aliphatic or heteroaliphatic moiety,

wherein R^i is an aliphatic or heteroaliphatic moiety;

R_5 is hydrogen, hydroxyl, protected hydroxyl or OR^{ii}, or an aliphatic or heteroaliphatic moiety,

wherein R^{ii} is an aliphatic or heteroaliphatic moiety, or wherein R_1 and R_5, when taken together, may form a cycloaliphatic or heterocycloaliphatic moiety comprising 6 to 12 atoms;

R_6 is hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R_7 is hydrogen, hydroxyl, protected hydroxyl, OR^{iii}, or an aliphatic or heteroaliphatic moiety,

wherein R^{iii} is an aliphatic or heteroaliphatic moiety;

R_8 is hydrogen, hydroxyl, protected hydroxyl or OR^{iv},

wherein R^{iv} is an aliphatic or heteroaliphatic moiety;

R_9 is hydrogen, $-CF_3$, -CHO, imine, hydrazone, oxime, carboxylic acid, carboxylic ester, acyl halide, ketone, amide, acetal, anhydride, dihalide, epoxide, nitrile or an aliphatic or heteroaliphatic moiety;

R_{10} is hydroxyl or protected hydroxyl;

R_{11} and R_{12} are each independently hydrogen, hydroxyl or OR^v, or an aliphatic or heteroaliphatic moiety, or, when taken together, may be –(C=O)-;

wherein R^v is an aliphatic or heteroaliphatic moiety;

and R_{13} and R_{14} are each independently hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, linear or branched, and whereby each of the foregoing aryl and heteroaryl moieties may be substituted or unsubstituted;

with the proviso that when R_4, R_5, R_8 and R_{10} are each hydroxyl, R_7 is hydrogen, R_{13} and R_{14} are each methyl, R_2 and R_3, taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:

(i) R_1 is methyl, R_9 is hydrogen, (R_{11}, R_{12}) is (=O) and R_6 is ethyl or isopropyl;

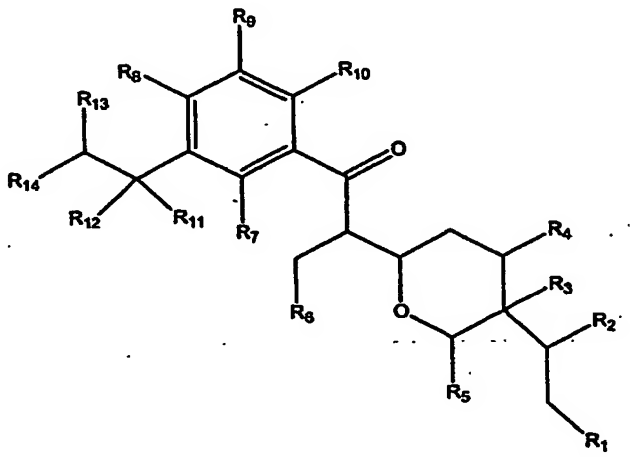
(ii) R_1 is methyl, R_9 is CHO, (R_{11}, R_{12}) is (OMe, H) and R_6 is ethyl, propyl or isopropyl;

(iii) R_1 is methyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl, propyl or isopropyl;

(iv) R_1 is methyl, R_9 is $COCH_3$, R_{11} and R_{12} are hydrogen and R_6 is ethyl; and

(v) R_1 is ethyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl.

45. The method of claim 43 wherein in the compound n is 1 and the compound has the structure:



46. The method of claim 43 wherein in the compound R_{10} is hydroxyl and the compound has the structure: